DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group 3 in the reply filed on June 16, 2009 is acknowledged. The traversal is on the ground(s) that the peptide of the prior art does not read on the instant claims. While the examiner agrees that the rationale provided previously is deficient, in that the applied art was an epitope of a larger protein, the claims lack unity for the following reason(s). Annex B, Part I(f) of the Administrative Instructions under PCT states that, "wherein a single claim defines alternatives (chemical or non-chemical)…the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature."

The alternatives must comply with subsections (i)(A) and one of either (i)(B)(1) or (i)(B)(2), which requires that, "all alternatives have a common property or activity" and "a common structure is present, i.e., a significant structural element is shared by all of the alternatives" (B)(1) or "in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains."(B)(2).

In the instant case, the method requires that the compounds have the same activity/function (CXCR4 antagonists, e.g. claim 60), satisfying requirement (A). However, the claim fails to satisfy either (B)(1) or (B)(2). Claim 40, as both originally presented and as currently amended, recites no structure sufficient to be considered "a common structure" or "a significant structural element [that] is shared by all of the alternatives", thus failing to meet the

requirements of (B)(1). The claim embraces an infinite number of potential peptides, sharing little or no structural similarity with any other compound within the genus.

Further, in looking to subsection (f)(iii), it is stated that 'recognized class of chemical compounds' means that, "there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved." One of skill in the art would not recognize these divergent compounds, or other compounds asserted to have said activity/function, as required, to function in the context of the instantly claimed invention. Thus, the claim fails to meet the requirement of (B)(2). The requirement is still deemed proper and is therefore made FINAL.

Claims 65-70 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 16, 2009.

Information Disclosure Statement

The listing of references in the specification (Page 89) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

The abstract of the disclosure is objected to because it is not descriptive of the invention claimed and references the claims and specification for definition of the claimed subject matter. Furthermore, the abstract asserts the compounds to be useful for treating or preventing condition that are generally considered to be unpreventable and/or difficult to treat, e.g. cancer and HIV infection. Correction is required. See MPEP § 608.01(b).

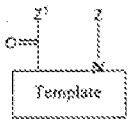
The amendment filed May 5, 2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant has substituted SEQ ID NO:1 P1' Lys to be Arg. The examiner is unable to find explicit, implicit or inherent support for this modification, and Applicant has provided no citation for support of the amendment.

Applicant is required to cancel the new matter in the reply to this Office Action.

Please note, the lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claim 40 is objected to because of the following informalities: Claim 40, the main independent claim is currently 30+ pages in length, and the arrangement of the variables in the claim would benefit from reordering.

The claims are directed towards compounds of the formula:  (I) , where Z^1 and Z are defined 24 pages later (in the current amendment). Z and Z^1 are defined as 4 and 6, or 5 and 7 residues, respectively, where the numbering of the residues starts at the attachment to formula (I) and numbers outward. The claim would have enhanced clarity if the compound were defined as in the specification, e.g. « Resin-P5-P4-P3-P2-P1-^{1}Pro-^{2}Pro-P1'-P2'-P3'-P4'-P5'-P6'-P7'; (Example 7, page 80, attached to a resin), in a linear manner. Furthermore, the claim defines the amino acids (starting at page 26) by their 'type', and indicates they may also be Gly, Pro "depending on their position in the chains". The definition of the variables C, D, E, F, H and I would benefit from being moved to after the proviso (starting at page 30) where the chains and their components are formally introduced. In making this amendment, Gly and Pro are defined as present only at certain positions and the phrase 'depending on...' would not be necessary.

Further, claim 40 recites non-standard, atypical amino acids in an abbreviated form. The first occurrence of non-standard abbreviations in the claim should be accompanied by their full name.

Claims 40 and 47-57 are objected to for the following minor informalities: the order of the amino acids should be presented in a manner that represents the peptide being described from left to right, as is standard convention. As currently recited, the positions are defined numerically, and does not immediately provide the reader with the appropriate order of the peptide.

Claims 59 and 60 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claims recite no structural variations in Formula (I) and do not limit the structure of the compounds. Further, all compounds of formula (I) are asserted by the specification to be CXCR4 inhibitors, and thus the claims are not further limiting.

Claims 52-57 are objected to for the following minor informalities: "and" should be placed between the last amino acid defined and the 'Cys at...'.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40 and 47-64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 is drawn to "compounds of formula (I)... and pharmaceutically acceptable salts thereof." It is unclear whether applicant is claiming a collection, e.g. an array, of compounds and their salts, or whether Applicant intended to claim "A compound… or a pharmaceutically acceptable salt thereof." This is further confused by the presence of dependent claims to "Compounds according to claim 40" (e.g. claim 47) and "A compound of formula I according to claim 40" (e.g. claim 52), which supports both positions.

In defining formula (I), Applicant defines  and -B-CO-, however the claim lacks a definition for -A-CO- or  . Further, it is unclear from formulae (a1) which carbonyl -B-CO- is defining, as B is attached to two carbonyls. Further, from the template, it is unclear whther the carbonyl attached to Z^1 is the peptide or -B-CO- carbonyl, and if the N attached to Z is the peptide or the  nitrogen. Additionally, it is unclear as to how the peptide Z and Z^1 are attached to the template.

Further, claim 40 recites a plurality of parenthetical expressions defining the variables, and it is unclear whether the parenthetical expressions are defining the variable, or are merely present as examples, and additionally some parenthetical expressions are missing closing brackets, leading to confusion as to where the expression ends.

Additionally, the claim reuses variables, e.g. R^{20}, multiple times, rendering the claim indefinite, as it is unclear which definition Applicant is intending to use. A variable should only be used once.

Furthermore, claim 40 allows for P^2 and $P^{2'}$ and/or P^4 and $P^{4'}$ to be a group of Type H. It is unclear whether all 4 together form a type H, or whether the compound can have two Type H compounds.

Additionally, claim 40 recites that $P^{7'}$ can have D-isomers, however Gly is the only defined amino acid, and the residues defined are "type E or type I", and there is nothing to suggest they are in the L-configuration. It is also unclear how I type, effectively Gly derivatives, can be D-isomers, having no chiral carbon.

Claims 40, 48 and 49 recite "or" between the last amino acid and the P2 and P2'

Claims 52-57 lack clear antecedent basis as "A compound of claim 1" is unclear as to whether it refers back to formula (I) or a portion of formula (I). Further, dependent claims, e.g. claim 52, should recite "The compound of" rather than "A compound" to refer back with proper antecedent basis.

Claim 58 lacks antecedent basis, in that claim 40 does not allow for enantiomers. Furthermore, it is unclear as to what Applicant is intending as the enantiomer of the compound, in that claim 40 only allows for an optional D-isomer amino acid at one position.

Claims 62-64 are drawn to "compositions", and it is unclear whether Applicant is claiming a set of compositions, or whether Applicant intended to claim "A composition".

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40, 47-49 and 58-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered in making the determination as to whether one skilled in the art would recognize that the applicant was in possession of the claimed invention as a whole at the time of filing include: (a) Actual reduction to practice; (b) Disclosure of drawings or structural chemical formulas; (c) Sufficient relevant identifying characteristics such as: (i) Complete structure, (ii) Partial structure, (iii) Physical and/or chemical properties or (iv) Functional

characteristics when coupled with a known or disclosed correlation between function and structure; (d) Method of making the claimed invention; (e) Level of skill and knowledge in the art and (f) Predictability in the art. While all of these factors are considered, a sufficient number for a *prima facie* case are discussed below.

Here, the claims are drawn to an infinite number of peptides of the general formula (I). The specification sets forth peptides within the genus, however they are so closely related in structure, they fail to provide description for the breadth of the genus claimed. Tables 1 and 2 set forth the peptides reduced to practice:

Sequ.ID	P6'	P5'	P4'	P3'	P2'	P1'	Template	P1	P2	P3	P4
SEQ ID NO:1	Arg	Arg	2-Nal	Cys	Tyr	Lys	^{D}Lys^{L}Pro	Tyr	Cit	Cys	Arg-NH_2
SEQ ID NO:2	Arg	Arg	2-Nal	Cys	Tyr	Lys	^{D}Lys^{L}Pro	Tyr	Cit	Cys	Arg-NH_2
SEQ ID NO 3	Arg	Arg	2-Nal	Cys	Tyr	Lys	^{D}Lys^{L}Pro	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO 4	Arg	Arg	2-Nal	Cys	Tyr	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cys	Arg-NH_2
SEQ ID NO:5	Arg	Arg	2-Nal	Cys	Tyr	Arg	^{D}Pro^{L}Pro	Tyr	Arg	Cys	Arg-NH_2
SEQ ID NO:6	Arg	Arg	2-Nal	Cys	Tyr	Arg	^{L}Lys^{L}Pro	Tyr	Cit	Cys	Arg-NH_2

and

Sequ.ID	P7'	P6'	P5'	P4'	P3'	P2'	P1'	Template	P1	P2	P3	P4	P5
SEQ ID NO:7	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:8	AcArg^{b}	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO 9	iPr^{b}Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:10	H-^{R}Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:11	H-Arg	Arg	Trp	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:12	H-Arg	Arg	Phe(4-NH$_2$)	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:13	H-Arg	Arg	Whe-3)Cys		Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO 14	H-(EA)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO 15	H-(PrA)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:16	H-(BA)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:17	H-(EGU)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{R}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:18	H-(PrGU)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:19	H-(BGU)G	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:20	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-OH
SEQ ID NO:21	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	(b1)-154	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:22	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	AMPA	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:23	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{L}Pro^{D}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:24	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2
SEQ ID NO:25	H-Arg	Arg	2-Nal	Cys	Tyr	Cit	Lys	^{D}Pro^{L}Pro	Tyr	Arg	Cit	Cys	Arg-NH_2

Beyond these compounds, the specification does not provide complete or partial structures for the peptides contemplated, the claims set forth only a partial structure for A and B and while the compounds are asserted to by CXCR4 antagonists, the art recognizes that amino acid substitution results in unpredictable results in activity, such that one cannot *a priori* predict the activity of a substitution. This knowledge in the art can be reasonably extrapolated to the

instant case, as one cannot determine *a priori* from the closely related compounds above that the plurality of structurally unrelated peptides would function as asserted by the disclosure, particularly since there is no structural core retained by the compounds. From the compounds of the disclosure, a clear common core is identified, however the claims breadth is beyond that which is exemplified; and while peptide synthesis is practiced in the art, the synthesis of the myriad of peptides claimed is beyond that of the artisan, with the expectation that they would function as disclosed.

Here, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lacks a sufficient variety of species to reflect this variance in the genus. While having written description of the compounds of claims 50-57 and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

40, 47-49 and 58-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making/using compounds of tables 1 and 2, does not reasonably provide enablement for making/using compounds beyond those disclosed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are discussed above, and are drawn generally to compounds of formula I, embracing a plurality of compounds.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

As discused above, the art recognizes that amino acid substitution results in unpredictable results on function. For example, RUDINGER (J. Rudinger. In: Peptide Hormones, JA Parsons, Ed. (1976) 1-7) teaches that, "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." (Page 6).

Further, MPEP § 2144.08 states, "The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior domains. James Darnell *et al.*, *Molecular Cell Biology* 51 (2d ed. 1990)."

(5) The relative skill of those in the art, (6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The artisan, while skilled in peptide synthesis, would not be able to synthesize compounds embraced by the claimed, particularly since the specification only provides guidance as to making the peptides described above, however it does not provide sufficient guidance with regards to making the myriad of non-standard amino acids embraced, nor how one would know which ones to make and use in the peptides claimed that would function commensurate with what is instantly disclosed and claimed (as CXCR4 antagonists).

Furthermore, given the unpredictability in the art, the specification fails to provide sufficient guidance as to how one would use the compounds as CXCR4 antagonists, when the art recognizes that there is unpredictability with regards to the function obtained by amino acid substitution in peptides.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to the unpredictable nature of amino acid substitution on the activity and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the

specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANDREW D. KOSAR whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Andrew D Kosar/
Primary Examiner, Art Unit 1654